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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/207,188	BLAKE ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80,81 and 83-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80,81 and 83-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 03/17/04 has been entered.

Applicants' After-final Amendment

2) Acknowledgment is made of Applicants' after-final amendment filed 03/17/04 in response to the Advisory Action mailed 11/05/03.

Status of Claims

3) No claims have been amended via the amendment filed 03/17/04.

Claim 84 has been amended via the amendment filed 10/09/03.

Claims 80, 81 and 83-93 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

6) The rejection of claim 82 indicated via paragraph 9 of the Advisory Action mailed 11/05/03 is moot in light of Applicants' previous cancellation of the claim. Reinsertion of claim 82 in paragraph 9 of the Advisory Action mailed 11/05/03 was due to an inadvertent error. As correctly indicated via paragraph 11 of the Office Action mailed 10/18/02, the rejection of claim 82 was considered moot previously.

Rejection(s) Maintained

7) The rejection of claims 80, 81 and 83-93 made in paragraph 15 of the Office Action mailed 01/11/02 and maintained in paragraph 13 of the Office Action mailed 04/09/03; paragraph 21 of the

Office Action mailed 10/18/02 and paragraph 9 of the Advisory Action mailed 11/05/03 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herebelow.

Applicants cite the various *Wands* factors and contend that the instant specification is enabling with respect to the scope of the claims. Applicants state that the specification provides sufficient direction and guidance needed to practice the invention. Applicants point to Examples 1, 6 and 7; and Table 4 of the specification, and state that the breadth of the claims is sufficiently supported by the specification and the state of the art. Applicants submit that the amount of direction provided is sufficient to enable the skilled artisan to administer the claimed conjugate containing the epitope responsible for inducing bacterial antibody production in a mammal in order to elicit antibodies that are protective against infection by group A streptococcal bacteria. Applicants assert that the instant invention relates to immunogenic compositions comprising group A streptococcal polysaccharide of formula (I) containing an epitope which induces the formation of bactericidal antibodies and to methods of eliciting antibodies specific to group A streptococcal polysaccharide by administering to a mammal a covalently bound polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate where the polysaccharide component is of Formula (I) and R is a terminal reducing L-rhamnose or D-GlcpNAc and n is 3-50, in an amount sufficient to provide protection against infection by group A streptococcal bacteria. Applicants contend that they have demonstrated how to make and use the conjugate; that group A polysaccharide antibodies are opsonic or bactericidal; how to administer the conjugate to mammals; and that the conjugate elicits protective effects. Applicants submit that from reading pages 12-18 of the instant specification, the skilled artisan would be capable of constructing the claimed conjugate, and that Example 6 specifically describes conjugating the oxidized GASP to either tetanus toxoid or human serum albumin. Applicants also state that experiments are demonstrative of the protective nature of antibodies directed to the group A streptococcal polysaccharide epitope. Applicants contend that experiments in the instant specification establish that: a) human sera contain group A polysaccharide antibodies; b) antibodies directed to the group A streptococcal polysaccharide epitope are protective, opsonic, or bactericidal; c) bactericidal assay testing of human sera at page 27 and Example 1 demonstrate that the group A polysaccharide antibodies promote opsonophagocytosis; d) Figure 4C

shows that the human serum killed organism growth; e) Figure 5 demonstrates that the human sera containing group A polysaccharide antibodies are opsonic in other serotypes. Applicants assert that undue experimentation is not needed to make or use the invention based on the content of the disclosure and the Declaration of Francis Michon. Applicants submit that the Michon Declaration demonstrates: a) the use of the group A streptococcal polysaccharide conjugate for immunization of rabbits; and b) the protection against a lethal challenge of live group A streptococci in mice given passively transferred specific antibodies from an immunized individual.

With regard to the polysaccharide used in the Sabharwal conjugate, Applicants point to item 13 of the Michon Declaration and state that the Sabharwal conjugate is within the scope of the claims. With regard to the lack of opsonophagocytic or absorption assay results raised by the Office for the sera obtained from conjugate-immunized mammals, Applicants state that they have provided several examples of the construction and use of the group A streptococcal polysaccharide-protein conjugates. Applicants submit that the instant specification at pages 19 and 20 describes that antibodies to group A streptococcus confer resistance to infection and that Table 4 shows high antibody titers resulting from immunization with the claimed conjugate. With this, Applicants conclude that vaccines of the claimed conjugate are useful in protecting against group A streptococcal infection.

Applicants submit that the opsonophagocytic or absorption assay described in the Examples of the instant specification is a model system for demonstrating protection against group A streptococcal disease. Applicants cite case law and assert that pharmacological or biological activity of a compound is relevant to a therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility, and that reasonable correlation may be evidenced by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence, or any combination thereof. Applicants cite *Nelson v. Bowler*, 526 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980) and state the following:

> Statistical certainty is not required when Applicants provide evidence that a correlation exists between a particular activity and an asserted therapeutic use of a compound, nor is actual evidence of success in treating humans where such a utility is asserted required. All that is required is a reasonable correlation between the activity and the asserted use.

Applicants' arguments have been carefully considered, but are non-persuasive. The instant

specification is enabling for a method of eliciting an immune response to group A streptococcal polysaccharide in a mammal comprising administering an effective amount of a purified group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50. However, the instant specification is not enabled for a method of eliciting a 'protective' immune response specific to group A streptococcal polysaccharide by administration of said conjugate, with or without an adjuvant, to a mammal, including a rabbit, human or a human child. Contrary to Applicants' assertion, Examples 1, 6 and 7; and Table 4 of the specification lack sufficient direction and guidance needed to practice the claimed method. The basis of the rejection previously set forth is reemphasized below.

Claims 90 and 91 are drawn to a method of eliciting 'protective' antibodies specific to group A streptococcal polysaccharide in a human, comprising administering to said human a polysaccharide-protein conjugate or a polysaccharide protein fragment conjugate, along with an adjuvant, wherein the conjugated polysaccharide is of formula (I) and wherein n is 3 to 50. Claims 80, 81, 83-89 and 92 are drawn to a method of eliciting 'protective' antibodies specific to group A streptococcal polysaccharide in a mammal, including a human and a human child, comprising administering to said mammal a polysaccharide-protein conjugate or a polysaccharide protein fragment conjugate, *without* any adjuvant, wherein the conjugated polysaccharide is of formula (I) and wherein n is 3 to 50. Thus, in this method, the recited conjugate comprising the polysaccharide of the recited structure and size is required to elicit 'protective' antibodies specific to group A streptococcal polysaccharide in a mammal, including a human and a human child, in the *absence* of an adjuvant. However, the instant specification lacks evidence showing that the recited conjugate elicits *in vivo* protection specific to group A streptococcal polysaccharide in any mammal, and lacks *in vitro* assay results that correlate with *in vivo* protective efficacy in a mammal.

A review of the specification and the evidence of record reveals the following. Neither the specification or the state of the art, as originally filed, nor the Michon Declaration or the Sabharwal abstract, provide enabling disclosure for the method claimed in claims 80, 81, 83-89 and 92.

A. State of the Art:

That natural antibodies to group A streptococcal carbohydrate, including IgG, are present in the sera of human adults and children was known in the art. See Shackelford *et al. J. Immunol.* 140:

3200-3205, 1988. However, the mere fact that a polysaccharide-containing product elicits detectable antibodies in a mammal does not mean that such antibodies confer protection. For example, whole streptococci, when injected into animals, readily produced precipitating group A streptococcal carbohydrate antibodies, but these antibodies failed to confer protection in an *in vivo* mouse protection model. See paragraph bridging left and right columns on page 593 of Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995).

At the time of the instant invention, those of skill in the art had already produced conjugates of isolated or purified native group A streptococcal polysaccharide. For instance, in 1984, Knigge *et al.* (*J. Clin. Microbiol.* 20: 735-741, 1984) conjugated an isolated and purified group-specific group A streptococcal polysaccharide to a protein carrier (see right column on page 735 of Knigge *et al.*). Some in the art had produced the group A streptococcal polysaccharide conjugates specifically for the purpose of immunizing rabbits and for inducing antibodies to group A streptococcal polysaccharide. For instance, in 1993, Gupta *et al.* (*Indian J. Med. Res.* A 97: 25-31, 1993) conjugated an isolated and purified native group A streptococcal polysaccharide to a protein carrier specifically for the purpose of immunizing rabbits. Gupta's group A streptococcal polysaccharide-protein conjugate when administered to rabbits in Freund's adjuvant elicited both monoclonal and polyclonal antibodies specific to group A streptococcal polysaccharide.

Group A streptococcal oligosaccharide was also conjugated to protein carriers prior to the instant invention. For instance, glycoconjugates of group A streptococcal polysaccharide of formula I wherein n=2 were known in the art and so also a method of administering the same to a mammal with an adjuvant to elicit group A streptococcal polysaccharide-specific antibodies. See the teachings of Reimer *et* al. *Carbohydr. Res.* 232: 131-142, 1992, especially the formula on page 141. Whether or not such group A streptococcal oligosaccharide conjugates had the capacity to elicit group A streptococcal polysaccharide-specific 'protective' antibodies was not predicted. In fact, a post-filing publication documented a lack of *in vitro* correlate of protection For example, Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995) teach that rabbits immunized three times with a Group A streptococcal polysaccharide (native) conjugated to tetanus toxoid and admixed with complete Freund's adjuvant, elicited group A streptococcal polysaccharide-specific antibodies measurable by ELISA. Salvadori *et al.* specifically teach that despite the fact that the conjugate administered along

with an adjuvant elicited group A streptococcal polysaccharide-specific ELISA antibody titers as high as 100,000, the resultant antibodies 'were not phagocytic'. Only sera from those rabbits which had anti-polysaccharide antibody ELISA titers of 1:200,000 or more were phagocytic for Group A streptococci. Another post-filing document published in 1995 could only speculate that a Group A streptococcal polysaccharide, i.e., non-depolymerized native A CHO, when conjugated to a protein carrier such as tetanus toxoid 'may be' an effective means of stimulating protective immunity against Group A streptococcal infections. See Michon *et al.* (*Canadian J. Infect. Dis.* 6: Suppl. C, July 1995). From these post-filing data, a skilled artisan would reasonably conclude that Salvadori's full length native GASP conjugate if administered to a mammal, without an adjuvant, is unlikely to elicit an ELISA anti-polysaccharide antibody titer that is equal to or more than 1:200,000 and therefore would not elicit opsonophagocytic or protective immune response against group A streptococci. Thus, contrary to Applicants' assertion, from the state of the art one of skill in the art would not expect Applicants' much shorter GASP of formula I having 3 to 50, or 3 to 30 repeat units, to elicit 'protective' antibodies against native group A streptococcal polysaccharide on conjugation to a protein or protein fragment, with or without a clinically acceptable adjuvant that is suitable for use in a human or human child.

Contrary to Applicants' assertion, in the instant case, there is lack of reasonable correlation between the pharmacological or biological activity of the recited conjugate having the recited formula and size, which lack of reasonable correlation is evidenced by the data of record documenting the lack of protective activity of the conjugate, the arguments or reasoning of record, and the supporting documentary evidence, or any combination thereof.

B. Facts from the Instant specification:

Since the state of the art reflects lack of correlation with protection and/or unpredictability withe regard to the protective nature of the group A streptococcal polysaccharide antibodies, one would look in to Applicants' disclosure for guidance and direction. Example 1 of the specification does not teach that antibodies to the polysaccharide of "formula I" wherein n is 3 to 50, or n is 3 to 30, are 'protective' against group A streptococci. Example 1 shows that Group A streptococcal infection caused by live streptococci induced variable levels of bactericidal group A carbohydrate antibodies in humans infected with these bacteria. However, infection induced opsonic antibodies

are known also include antibodies with M protein-specificity (see Fischetti V. *J. Immunol.* 130: 896-902, 1983). Example 1 shows that not all sera from group A streptococcus-infected patients contain a geometric mean group A streptococcal carbohydrate antibody titer of >200,000. Example 1 shows that live whole cell group A streptococci, upon natural infection in humans, induced a geometric mean bactericidal antibody titer of >200,000 in some infected patients. The specification, on page 17 at lines 22 and 23, recognizes that such whole cell streptococci are **not** desirable for use as a vaccine. This is well supported in the literature by those of skill in the art. For instance, the art showed that whole streptococci, when injected, readily produced precipitating group A streptococcal carbohydrate antibodies, but these antibodies failed to confer protection in an *in vivo* mouse protection model. See paragraph bridging left and right columns on page 593 of Salvadori *et al.* (*J. Infect. Dis.* 171: 593-600, 1995).

The bactericidal data from Example 1 of the instant specification is not relevant since the claimed method does not involve administration of live or killed streptococcal cells to a mammal, human or a child. The infection-induced antibodies in the human sera were induced by the non-isolated, native and non-depolymerized GASP presented to the host immune system on the surface of live whole cells of streptococci. The specification in the last paragraph of page 8 states that a CHO antibody titer of >200,000 (i.e., antibodies induced by group A streptococcal infection) represents 80% killing in the bactericidal assay. However, this bactericidal assay was performed with the sera of humans who were **not** immunized with the polysaccharide of formula I (wherein n=3 to 50, r n=3 to 30) conjugated to a protein or a protein fragment, as recited in the instant claims. The immunogen recited in the instant claims is not live whole cell group A streptococcus, but a polysaccharide of formula I (wherein n is 3 to 50, or 3 to 20) conjugated to a protein or a protein fragment after modification or treatment of the polysaccharide with several chemicals during the process of oxidizing and conjugating of the polysaccharide. In order for formula I polysaccharide-protein conjugate, or formula I polysaccharide-protein fragment conjugate of the instant invention to be used in a method of eliciting a GASP-specific 'protective' immune response in a mammal, the recited conjugate (and **not** the live whole cell Group A streptococci), with or without a clinically acceptable adjuvant, is **required** to induce 'protective' antibodies specific to group A streptococcal polysaccharide, or a geometric mean level of ELISA GASP antibodies in a mammal immunized with

the conjugate (as opposed to live whole cell Group A streptococci), which antibody level is correlative of 'protection'. It should be noted that no evidence is of record in the instant disclosure establishing that the broadly recited n range of 3 to 50, or 3 to 30, is critical for the invention, i.e., for induction of 'protective' immunity. This is important because: a) predictability or unpredictability is one of the *Wands* factors for enablement; and b) the art has established that antibodies elicited even by a full length group A streptococcal polysaccharide, exposed on streptococci, cannot be predicted to be 'protective' in an *in vivo* mouse model, or via *in vitro* correlative assays.

Example 6 of the instant invention describes how to produce a group A streptococcal polysaccharide conjugate wherein the polysaccharide has an assumed molecular weight of 10 kilodaltons, i.e., n=20. As set forth in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17), Example 7 and Table IV show that rabbits immunized with the isolated native and unconjugated GASP elicited a geometric mean base line anti-GASP ELISA titer of $\leq$100 even after three immunizations. After the first immunization, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., n=about 20) and covalently coupled to tetanus toxoid protein induced the same base line titer of GASP antibodies (i.e., $\leq$100) in rabbits as that elicited by the uncoupled native GASP. This conjugate in saline elicited measurable GASP antibody titers by ELISA after the second and third immunizations. However, the geometric mean ELISA titer elicited by the conjugate was nowhere near 200,000. Even when rabbits were immunized with this GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, the geometric mean ELISA titer elicited after three immunizations was nowhere near 200,000. Clearly, the claimed method of eliciting 'protective' antibodies specific to GASP in a mammal by administration of a formula I GASP-protein conjugate wherein n is about 20 (much less a formula I GASP-protein fragment conjugate wherein n= 3, 4 or 5), with or without a clinically acceptable adjuvant, is not enabled. Rabbits immunized with the formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA, elicited a geometric mean ELISA antibody titer that exceeded 200,000 following the second and third immunizations. However, it is important to note that CFA and IFA are not acceptable in the art of vaccines for use in a human or a human child. There is neither any showing, nor is it predictable that one skilled in the art can reproducibly and successfully practice the claimed method by administering to a mammal, human or a child, a

formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate wherein n is 3 to 50. No opsonophagocytic or absorption assay results with the sera obtained by immunizing a mammal with the conjugate recited in the instant claims have been disclosed. No evidence is of record in the instant disclosure establishing that the recited n range of 3 to 50, or 3 to 30 is critical for the claimed invention, i.e., for induction of protective immunity. There is no data correlating GASP of one or more size that falls within the broadly recited range of n=3 to 50 to induction of 'protective immune response'. Thus, Applicants' own specification provides *prima facie* evidence for a lack of scope of enablement for the claimed method.

C. The Michon Declaration:

The Michon Declaration mainly discusses the post-filing data from the Sabharwal abstract, which has been fully analyzed below at section D. The Michon Declaration at paragraph 13 asserts that the instant application and the Sabharwal abstract describe a method of eliciting group A streptococcal antibodies by administering polysaccharide-protein conjugates. The Declaration submits that the one skilled in the art would be capable of reproducibly and successfully practicing the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate where n is 3 to 50, or n is 3 to 30, without undue experimentation. However, contrary to what is asserted in paragraph 13 of the Michon Declaration, whether or not one skilled in the art would be capable of reproducibly and successfully practicing the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate where n is 3 to 50, or n is 3 to 30, without undue experimentation, is not the issue. The issue is whether or not one skilled in the art would be capable of reproducibly and successfully practicing a method of administering a formula I GASP polysaccharide-protein or formula I GASP polysaccharide-protein fragment conjugate wherein n is 3 to 50, or 3 to 30, or wherein the polysaccharide has a molecular weight of about 10 kilodaltons to elicit 'protective' immune response against GASP.

D. The Sabharwal Abstract:

The Sabharawal abstract provides data showing that active immunization of mice with native group A streptococcal polysaccharide of undisclosed structure, A CHO, conjugated to tetanus toxoid, protected mice against infection with specific types of group A streptococci, **only** when

administered along with an adjuvant, such as, alum. The group A streptococcal polysaccharide present in the Sabharwal conjugate is not disclosed as having the same formula, as the one recited in the instant claims, wherein the structure of the polysaccharide has formula I with n being 3 to 50, or 3 to 30, but is referred to as 'Group A CHO'. The Sabharawal native group A streptococcal polysaccharide conjugate elicited protective immunity in mice **only** when administered in alum. Contrary to Sabharwal's teachings, the method of instant claims 80, 82-89, 92 and 93 uses a polysaccharide of a specific formula and specific size conjugated to a protein or a protein fragment, *in the absence of an adjuvant*. Therefore, while the Sabhrawal abstract demonstrates the protective efficacy of a full length group A streptococcal polysaccharide of undisclosed formula conjugated to tetanus toxoid, **only** when administered with alum, it does not provide evidence enabling a method of eliciting protective antibodies specific to group A streptococcal polysaccharide in a mammal, including a human or human child, by administration of a group A streptococcal polysaccharide of the specifically recited formula I, wherein n=3 to 50, or n=3 to 30; or wherein the polysaccharide has a molecular weight of about 10 kilodaltons, conjugated to a protein or a protein fragment, *with or without an adjuvant*. Even with regard to the native group A streptococcal polysaccharide of undisclosed structure, the Sabharwal data supports the observation described in Example 7 of the instant specification in that induction of polysaccharide-specific antibodies requires the administration of the Sabharwal A CHO conjugate *along with an adjuvant*. Assuming, *arguendo*, that the Group A CHO in the conjugate of Sabharwal's disclosure has a size and structure that falls within the scope of that recited in the instant claims, even then, the method as claimed in claims 80, 81, 83-89, 92 and 93, of eliciting protective antibodies specific to group A streptococcal polysaccharide in a human or non-human subject comprising administering the recited conjugate *without an adjuvant* is not enabled.

Conclusion

In sum, the instant specification is enabling for a method of eliciting an immune response to group A streptococcal polysaccharide in a mammal comprising administering an effective amount of a group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50. The instant specification, the knowledge from the state of the art, the Michon Declaration, and the Sabharwal abstract, alone or in combination, do **not** enable a

method of eliciting a 'protective' immune response specific to group A streptococcal polysaccharide in a mammal (including a rabbit, human or a human child) as claimed comprising administering, *with or without an adjuvant*, an effective amount of a group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50, or 3 to 30, or wherein the polysaccharide has a molecular weight of about 10 kilodaltons. Absent evidence to the contrary, the rejection stands.

Contrary to Applicants' assertion, in the instant case, there is lack of reasonable correlation between the pharmacological or biological activity of the recited conjugate having the recited formula and size, which lack of reasonable correlation is evidenced by data of record documenting the lack of protective activity of the conjugate, the arguments or reasoning of record, and the supporting documentary evidence, or any combination thereof. With regard to enablement, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) recognizes the following:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 **unless there is a reason to doubt the objective truth** of the statements contained therein which must be relied on for enabling support. [Emphasis added].

In the instant case, the specification, the Michon Declaration, and the data from both the post-filing references of Salvadori *et al.* and Sabharawal *et al.* provide the *prima facie* evidence to doubt the objective truth of the statements contained in the specification and the claims.

Rejection(s) under 35 U.S.C. 112, Second Paragraph

8) Claims 80, 81 and 83-93 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 80 lacks proper antecedent basis in the second recitation of 'a mammal' (see line 2). Since there is already an earlier recitation of 'a mammal' in the claim, for proper antecedence, it is suggested that Applicants replace the recitation with --said mammal--.

(b) Claim 80 lacks proper antecedent basis in the second recitation of 'or protein fragment' (see line 2 under the chemical structure of formula I). Since there is already an earlier recitation of 'a ... protein fragment' in the claim, for proper antecedence, it is suggested that Applicants replace the recitation with --or said protein fragment--.

(c) Claim 91 contains the trademark/trade name "QS21". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982)*. The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe QS21 and, accordingly, the identification/description is indefinite.

(d) Claims 81 and 83-93, which depend directly or indirectly from claim 80, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Remarks

9) Claims 80, 81 and 83-93 stand rejected.

10) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

11) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

12) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week,

which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June, 2004

SD.
S. DEVI, PH.D.
PRIMARY EXAMINER